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POLICY AND POLITICS

Seventy-five percent of Canadians secure reimbursement of Alzheimer's drug

by Hannah Hoag

Alzheimer's disease is the most common form of dementia. The disease currently affects over 220,000 Canadians and is expected to increase affecting over 750,000 Canadians by 2030. In Quebec, 40,000 to 45,000 individuals have Alzheimer's disease.

The cognitive decline associated with Alzheimer's disease is progressive and variable; 6 to 10 years pass between diagnosis and death. At autopsy, the brains of patients with Alzheimer's disease commonly show low levels of acetylcholine (ACh) due to a loss cholinergic neurons. Cholinergic neuronal loss affects a myriad of brain functions. Language, motor skills, judgement, abstract thinking, behaviour, personality, and memory all deteriorate, literally robbing the patients of their character.

(Continued on page 2)

DOES STRESS INFLUENCE THE COURSE OF AGING?

The research of Dr. Michael Meaney, Professor, Faculty of Medicine, McGill University and Associate Director of Research, Douglas Hospital Research Centre.

by Alison McTavish

With papers published in both Nature Neuroscience and Science, Dr. Michael Meaney is continuing a Montreal tradition of ground-breaking research in stress. "We are the city of Hans Selye and Donald Hebb," says Meaney, "and the early work of Selye is one of the key components of my interest." Selye was a pioneer in stress research, while Hebb revolutionized psychology with his work on learning and perception.

Meaney, currently Associate Director of Research at the Douglas Hospital and a full professor in the Faculty of Medicine at McGill, first became interested in stress as an undergraduate at Loyola College. His interest intensified while studying for a PhD in endocrinology in Concordia University's psychology department, and during a postdoctoral fellowship with Dr. Bruce McEwen at Rockefeller University in New York. More specifically, Meaney is interested in individual differences in response to stress. "We constantly looked for the consequences of stress as if they were universal," he explains, "we wanted to build on work done in the 1960's and try to understand how individual differences in stress responses



occurred."

During the 1980's, Meaney and his team looked at individual differences in stress responses to see if they would affect the course of aging. Their work was based on the notion that stress hormones contribute to the degeneration of the hippocampus, the brain region responsible for the learning of new information. "We reared animals under different conditions that either accentuated or dampened their reactivity to stress, and we found that as the animals aged the ones with the more prominent stress response were more affected over the course of aging." Stress appears to accelerate the pace of brain aging, and can result in the loss of neuronal function and even the loss of brain cells.

Having documented that individual

(Continued on page 2)

PUBLIC LECTURE SERIES

The Chemistry of Aging

by Jeff Boyczuk

Searching for the fountain of youth? You're certainly not alone. Proof of this could be found in the overflow crowd at Dr. Joe Schwarcz's recent talk, "The Chemistry of Aging", sponsored by the McGill Centre for Studies in Aging, and

held at the Montreal Delta Hotel.

Schwarcz is the director of McGill's Office for Chemistry and Society, dedicated to conveying scientific information to educators, students and the public in an accurate and understandable fashion. He also

(Continued on page 3)

IN THIS ISSUE

THE CHEMISTRY OF AGING	1
REIMBURSEMENT OF ALZHEIMER DRUGS	1
EFFECT OF STRESS ON AGING	1
WE ARE LIVING LONGER AND FASTER	5
OSTEOPOROSIS AND ESTROGEN IN MEN	5
AGING-RELATED WEBSITES	6

Seventy-five percent of Canadians secure reimbursement of Alzheimer's drug

(Continued from page 1)

Caring for a patient with Alzheimer's disease becomes a costly and emotionally strenuous endeavour. The healthcare system spends an estimated \$3 billion dollars per year to care for patients with Alzheimer's disease. However, many patients with Alzheimer's disease are not cared for in the healthcare system, but by caregivers who are family members. Many of the caregivers suffer from caregiver stress, which leads to emotional and mental distress.

Alzheimer's disease is a costly disease because it cannot be cured. The medications that are currently available can only alleviate the symptoms, and most of these medications are not available in Canada. One Alzheimer's drug approved for use in Canada is Aricept (donepezil). Aricept is an acetylcholinesterase inhibitor that increases the concentration of ACh in the brain. Aricept will not cure the patient of Alzheimer's disease, but may delay or decelerate disease progression in patients who have been diagnosed with mild to moderate forms of Alzheimer's disease. These patients may live longer and benefit from future medications, or may live at home or with a family member longer and enter a nursing home later, reducing medical costs. Aricept may delay the progression of Alzheimer's disease by 1 to 1.5 years in patients with mild to moderate Alzheimer's disease.

Whereas nursing home costs for a

(Continued on page 3)

The research of Dr. Michael Meaney, Professor, Faculty of Medicine, McGill University and Associate Director of Research, Douglas Hospital Research Centre.

(Continued from page 1)

differences in stress responses do indeed occur, the next step was to understand the events that would give rise to such individual differences. This led Meaney's group to look at maternal behavior. "We believed that the most potent source of individual differences would emerge from maternal care, and of course it did turn out to be a factor that greatly influences the way an animal responds to stress."

Apparently maternal care has a profound effect on the hypothalamus. The hypothalamus is the area of the brain that controls the magnitude of the stress response, and is the hub of all endocrine events. "The way your heart, your liver and your hormones respond to a stressor is all determined by the amount of corticotropin releasing factor (CRF) released by your hypothalamus," he explains. CRF triggers the release of stress hormones from the adrenals, catecholamines (noradrenaline) and glucocorticoids (cortisol). These hormones cause metabolic and cardiovascular changes that prepare the body to deal with the challenge of the stressor.

If more CRF is produced, more stress hormones are released and the response will be greater. Over the course of development, it appears that maternal care literally programs the development of the hypothalamus, and determines, in the rat at least, how much CRF is produced. "You end up with a situation where the hormones released by the hypothalamus are permanently influenced by the quality of maternal care," says Meaney.

Evidence indicates that one class of stress hormones, the glucocorticoids, can produce cognitive deficits in both aged animals and aged humans. Glucocorticoids compromise the function of neurons in the cortex and hippocampus, brain regions that are of critical importance for learning and memory, and particularly for learning new information. Damage in these areas in both humans and animals leads to learning impairments.

However, the news isn't all bad because cortisol and noradrenaline have the opposite effect on another brain region, the amygdala. The hormones actually enhance the storage of information in this area. "This makes perfect sense," says Meaney, "because the amygdala is involved in emotional learning, and obviously during a period of stress you'd like the individual to be learning the most biologically relevant information. And that's

information about the stressor."

Meaney admits that his interest in aging is secondary to his interests in individual differences. "I was particularly interested in showing that individual differences had functional importance to health," he says. "When you start working with elderly individuals, the system is very dynamic and so you see the consequences of these types of individual differences much more dynamically than you do at any other stage in the life cycle."

Recently Meaney has also been involved in the Montreal Consortium for Brain Imaging Research (MCBIR). He describes his role as a facilitator, and notes that thanks to Dr. Bruce Pike and Dr. Alan Evans (both key members of McGill's McConnell Brain Imaging Centre), McGill has a remarkable human aging and human neuroimaging program. Over the past five years, however, they've been frustrated by a lack of funding. "People would come from all over to the program and be stunned by the lack of resources," says Meaney. A substantial grant from the Canadian Foundation for Innovation this past year has changed all that (see the September 2000 issue of Geronto-McGill), and now the MCBIR is a reality. Meaney and his group at the Douglas Hospital are able to collaborate with researchers at the Montreal Neurological Institute. "We can focus our attention on the science, without having to worry about the hardware."

What does the future hold? "What interests me is trying to push the level of individual differences a little higher up in the system. In our collaborations with Dr. Sonia Lupien (Head of Research on Aging and Alzheimer's Disease at the Douglas Hospital Research Centre) we're looking at how individual differences in the way people perceive stressors can influence the course of the aging process." He notes that animal models, like the rats he has worked on in the past, are only effective up to a point. "We can't look at more subtle differences, how people respond and perceive stressors." That will involve looking at the frontal cortex of the brain, an area very different in the human and the rat. In addition, he would like to see how cognition and perception influence the course of aging. "I'd like to do something in humans," he says, "that really takes advantage of the species." ■

Seventy-five percent of Canadians secure reimbursement of Alzheimer's drug

(Continued from page 2)

patient with Alzheimer's disease approach \$35,000 per year, a prescription for Aricept costs approximately \$5 per day (\$1,700 per year). Five Canadian provinces - Quebec, Ontario, Manitoba, Saskatchewan, and Alberta - currently offer reimbursement to patients who use Aricept and who meet selected criteria.

In June 1999, Ontario became the first province to offer reimbursement for Aricept under the Ontario Drug Benefit Program. Manitoba Health announced that it too would add Aricept to its benefit list, and Alberta placed Aricept on the Alberta Health and Welfare Drug Benefit List (AHWDBL) on December 1, 1999. When Alberta added Aricept to the AHWDBL, 1,100 Albertans paid for the medication, and an additional 6,000 Albertans who were not taking the Aricept could benefit from it. Quebec and Saskatchewan added Aricept to their individual drug reimbursement programs in 2000. Saskatchewan estimates that 1 in 5 patients with Alzheimer's disease will benefit from using Aricept.

To qualify for reimbursement, a patient must have a diagnosis of mild-to-moderate probable Alzheimer's disease (Alzheimer's cannot be definitively diagnosed until after death, at autopsy, therefore all diagnoses are referred to as probable). Cognitive and functional evaluations may also be used to establish eligibility for reimbursement. The patient's cognitive and functional abilities are determined with the Mini-Mental State

(Continued on page 4)

PUBLIC LECTURE SERIES

The Chemistry of Aging

(Continued from page 1)

attempts to demystify chemistry for the Montreal public through a weekly call-in radio show on CJAD, regular appearances on the Canadian Discovery Channel, and in Saturday column for the Montreal Gazette.

Interest in slowing down the aging process is not a modern phenomenon. Schwarcz began his talk by noting that even biblical King David worried about his increasing age. Unfortunately, scientific investigations into the aging process hadn't come about at this time, and the only advice offered to the King was to "lie with young virgins".

Schwarcz dived into more scientific forays with a discussion of the work of eminent 19th century French physiologist Édouard Brown-Sequard. Observing that sexual activity in animals decreased with age, Brown-Sequard wondered whether depletion in levels of sex hormones might be at the root of the aging process. He investigated this possibility by injecting elderly guinea pigs with a solution made from the extracted testes of young male pigs, and reported that the elderly pigs showed renewed vigor. Taking it a step further, he tested this theory in humans by using himself as a subject. At the age of 78, Brown-Sequard injected himself with extracts from monkey glands (he was unable to find a willing human testes donor), and claimed to have felt revitalized. Although modern scientific thought questions the validity of his results, Brown-Sequard's work did draw attention to the important relationship between hormonal changes and human aging.

Schwarcz also discussed more contemporary research in hormone therapy, concentrating on the history of work with human growth hormone (HGH). HGH is produced by the pituitary gland and is, as the name implies, responsible for growth.

Research has shown that levels of HGH in the bloodstream decrease with age, suggesting an obviously link to the deterioration of body structures. Following this logic, initial research in the 1980s showed benefits of HGH injections on men in their 80s, with increases in muscle mass, a thickening of the skin, and reports of more energy. However, it soon became apparent that HGH wasn't a wonder cure for the effects of aging. Six months into the first study, test subjects reported an arthritic type of soreness in their hands. Subsequent research found this to be a common side-effect, and further revealed that increasing levels of HGH might also facilitate undesirable growth of human tissue, such as tumors. Research continues on HGH and, with the jury still out, Schwarcz recommends waiting for a clear verdict before considering any HGH-based treatment as a plausible anti-aging strategy.

Of all the anti-aging treatments on the market today, perhaps some of the grandest claims come from proprietors of herbal remedies. Schwarcz reviewed the somewhat sparse evidence of the effectiveness of herbal preparations such as ginkgo biloba and ginseng. Ginkgo biloba, an extract from the ginkgo tree, is widely promoted as a memory-enhancing product. Some studies have suggested that ginkgo does enhance short-term recognition memory, but Schwarcz noted that it is unclear how long the effects last or if the results might be of any practical significance. Likewise, claims of the numerous health benefits from ginseng stem more from a long history of usage by the Chinese, rather than rigorous scientific testing.

One of the major problems with herbal remedies and other natural health products is that the industry is currently unregulated in

(Continued on page 4)

Seventy-five percent of Canadians secure reimbursement of Alzheimer's drug

(Continued from page 3)

Examination (MMSE) and the Functional Activities Questionnaire (FAQ). In Saskatchewan and Ontario, a patient must score between 10 and 26 on the MMSE to be considered for the reimbursement program.

Once diagnosis and evaluation are complete, a patient may be prescribed Aricept for a 3-month trial period. The patient must show an improvement from their initial MMSE or FAQ scores to continue treatment. Treatment continues providing MMSE or FAQ scores do not decline substantially.

Pfizer Canada, which is responsible for the manufacturing and marketing of Aricept in Canada, has agreed to help support the reimbursement program (in Alberta) by providing newly diagnosed patients with mild to moderate Alzheimer's disease with Aricept for the initial 12 weeks of treatment.

With Alberta, Manitoba, Saskatchewan, Ontario, and Quebec offering reimbursement for Aricept, approximately 75% of Canadians have access to the first Alzheimer's medication to be approved in Canada. ■

PUBLIC LECTURE SERIES The Chemistry of Aging

(Continued from page 3)

Canada, says Schwarcz. As a result, different makers will produce remedies with different chemical compositions, and different levels of the active ingredients. Furthermore, the active ingredients in some products, such as ginkgo biloba, have yet to be definitively identified. While Schwarcz suggests that modest consumption of herbal remedies such as ginkgo and ginseng aren't likely to have any negative side effects, he stresses that solid evidence backing up manufacturer claims of anti-aging properties is lacking in most cases.

If you're starting to feel that there is no panacea for aging, you're probably right. But while Schwarcz deflated hopes about magical hormonal treatments and miracle herbal concoctions, he did offer some encouraging news about a dietary supplement that is easily obtainable, relatively inexpensive, and has been shown to fight certain diseases associated with aging. This is none other than vitamin E.

There is a body of research linking vitamin E intake to reduced incidences of certain types of cancer and heart disease, says Schwarcz. With the major food source of vitamin E being nuts and oils, it is unlikely that most people will get enough vitamin E to garner these benefits, so he suggests taking a daily supplement of between 200 and 400 international units.

Schwarcz also recommended certain dietary choices that may increase health and longevity. In particular, he advocates a diet rich in antioxidants, which fight diseases such as cancer. The easiest way to achieve this, of course, is to increase the amount of fruit and vegetables in your diet. One fruit that is particularly rich in antioxidants is blueberries. You can also enhance your antioxidant intake by choosing any variety

of black tea over coffee.

But what may be the most important dietary means to increasing longevity is also likely the most distressing for many people. As it turns out, animal studies have shown that one incredibly effective way of increasing life-span is to reduce caloric intake. Test animals that are put on a low-cal diet seem to be more energetic, thinner, and easily outlive their regular diet counterparts, said Schwarcz. One theory about why this is so proposes that a reduced-calorie diet slightly lowers the body's temperature. This, in turn, slows down the chemical changes within the body, which constitute the aging process. While it is not as easy to gauge whether the effects seen in animals would be as dramatic for humans, some researchers suggest humans might also increase their longevity by cutting back on their caloric intake. However, Schwarcz wryly notes that such a practice only supports the old adage that "the only thing that you have to do to live longer, is to give up everything worth living longer for".

And this statement seems to sum up the theme of the lecture. There is no single wonder treatment to stop the effects of aging, let alone reverse them. There are certainly choices that can be made which lead to a healthier lifestyle, and possibly a longer life. But Schwarcz's best advice seems clear. If you do choose to take up the struggle against the aging process, don't forget to enjoy the life you do have to live.

Dr. Joe Schwarcz is Director of the McGill's Office for Chemistry and Society. ■

Osteoporosis: Estrogen is the key for both men and women *by Alison McTavish*

Although it's been known for a long time that estrogen is important for skeletal health in women, a new study provides evidence that estrogen also regulates bone resorption in normal elderly men.

Both men and women experience an age-related decline in bone mineral density starting in mid-life. Resorption, the normal process of bone breakdown, occurs throughout the lifespan as bones continually break down and regenerate. During aging, the equilibrium of this process shifts resulting in more resorption and less regeneration.

For women, sustained production of estrogen is essential for the maintenance of bone mass. During menopause, women experience a dramatic and sudden loss of estrogen and consequently they begin to lose bone mineral density. If osteoporosis develops, women are often treated with estrogen replacement.

In comparison, men lack the rapid phase of bone loss associated with menopause in women. Instead they experience a constant and more gradual loss of bone mass as levels of both testosterone and estrogen decline over the course of their lives. Because testosterone is the dominant sex steroid in men, it has always been thought that testosterone regulated bone metabolism in men. Evidence from Dr. Sundeep Khosla's group at the Mayo Clinic contradicts this belief.

Khosla's group studied 59 elderly men, with an average age of 68 years. The men were studied first under conditions of estrogen and testosterone replacement. After a baseline was established, they were divided into four subject groups. One group received no hormones, while the other groups received testosterone alone, estrogen alone, or both estrogen and testosterone.

The investigators found that estrogen played the key role in preventing the increase in bone resorption that occurred when both testosterone and estrogen were withdrawn. Men who received no hormones or testosterone alone, however, showed significant increases in bone resorption. These findings will further our understanding of bone metabolism, and may help in the development of approaches for the treatment or prevention osteoporosis in men.

References:

1. Alireza Falahati-Nini et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest* 2000; 106(12):1553-1560.
2. NIH Consensus Statement. Osteoporosis prevention, diagnosis and therapy. March 2000.

WE'RE LIVING LONGER – FASTER *by Jeff Boyczuk*

It's no secret that people today are, on average, outliving their 19th century counterparts, thanks largely to advances in medical science and public sanitation. At the same time it's not as clear whether maximum life-span – the age at death of the single longest-living person in a generation – has also increased. A popular belief among scientists is that the human life-span is biologically limited, and that this hypothetical maximum age will not increase over time. However, a recent study investigating 139 years of Swedish mortality data suggests that human life-span is increasing and, in recent years, at an accelerated pace¹.

Difficulties in gauging the historical trend of maximum life-span arise from the poor quality of public record keeping prior to the 20th century, coupled with a tendency for reported cases of extreme longevity to be exaggerated. Among industrialized countries, Sweden's statistical records prove to be an exception, providing exceptionally accurate mortality data back to the mid-1800s. Using Sweden as a test case, a group of demographers led by J.R. Wilmoth of the University of California, Berkeley, examined the trend of extreme human longevity between 1861 and 1999.

The group charted the maximum age at death in each year of the 139-year period and found that the longest lives of Swedes hovered around 101 years in 1861, and increased to about 108 years in 1999. By performing what is known as a regression analysis, the researchers determined that maximum life-span increased at .44 years per decade until 1969, then increased more rapidly at 1.11 years per decade between 1970 and 1999.

One potential cause of this increase in longevity might stem from larger birth groups in the 20th century. Simply through the principles of probability, a larger population provides a greater chance that some individual will live to an extremely old age. To ensure that the observed increase in Swedish life-span was not just a function of larger modern populations, the data was reexamined by considering the size of the birth cohorts for the years between 1756 and 1884, as well as the death rates at each year of life from age 0 to age 119. This analysis revealed that over 70% of the observed increase in the Swedish maximum life-span was attributable to lower death rates above 70 years, and only 12% of the increase was attributable to a greater number of births. In other words, an increase in life-span was largely due to elderly people living to older ages. This trend has been

observed by demographers since the 1970s, and is the reason for the acceleration in the rate of increase of maximum life span since 1969.

While the Swedish data suggest that human life-span is increasing, unfortunately reliable demographic data over the same time period from North America or western European countries is not available to reinforce this finding. Nevertheless, since the mortality history of Sweden seems quite similar to that of western countries, Wilmoth et al. propose that a similar trend might be found in other industrialized countries. In any case, while the Swedish data does not absolutely refute the idea of an unchangeable life-span, it does suggest that if a maximum human age does exist, we have yet to see it.

¹Wilmoth, J.R., Deegan, L.J., Lundstrom, H., Horiuchi, S. Increase of maximum life-span in Sweden, 1861-1999. *Science* 2000; 289: 2366-2368. ■

REGISTRY OF AGING-RELATED WEBSITES

by Hannah Hoag



www.uwo.ca/actage

The Centre for Activity and Ageing is a multicentre cooperative located at Mount St. Joseph in London, Ontario. The Faculties of Health Sciences and Medicine & Dentistry at the University of Western Ontario and The Lawson Research Institute of the St. Joseph's Health Centre merge kinesiology, medicine, physiology, biostatistics, biochemistry, physiology, and sociology as it relates to physical activity and aging.

www.asaging.org

The American Society on Aging is a professional organization that addresses the complexity of aging by forming a multidisciplinary group to improve the knowledge and understanding of aging. The ASA offers education and training programs through seminars, web-based computer training and teleconferences, and a searchable database of resources.

www.cnn.com/health/aging

CNN.com's aging website offers the latest headlines and news stories related to aging and aging research. It offers numerous links to other websites that describe age-related conditions, provides a doctor Question & Answer forum, and provides users with hints to cope with some of the problems commonly associated with aging.

www.cdc.gov/nchs/agingact.htm

The National Center for Health Statistics website is produced and maintained by the US Federal Government. The aging portion of the site is divided into 3 major subsections: Aging Activities, Links to Other Sites, and News Flashes. Aging Activities is the most prominent portion of the site, providing access to a Trends in Health and Aging database of statistics, a set of Longitudinal Studies on Aging Surveys, and a link to the Federal interagency Forum on Aging-Related Statistics.

These websites are presented as reference tools for readers. Geronto-McGill does not guarantee the accuracy of information found at these sites, nor endorse any of the products found therein.

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